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LENTICULE
IMPLANTATION AND
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NEW APPROACH IN
TREATMENT OF
ADVANCED
KERATOCONUS
DISEASE**



CASE REPORT

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FRESH CORNEAL LENTICULE IMPLANTATION AND AUTOLOG SERUM -NEW APPROACH IN TREATMENT OF ADVANCED KERATOCONUS DISEASE-CASE REPORT

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Abstract

Purpose:

The aim of our study is to investigate the feasibility and the effect of fresh lenticule implantation as allogenic graft that will be taken from myopic patients to implant in patients with keratoconus disease using VisuMax Femtosecond laser-Smile module surgery with primary objective to increase central corneal thickness and secondary to improve visual acuity and reduces K-values and to show the autologous serum drop improve the recovery of patients with mild dry eye in keratoconus disease.

Case:

A 19-year-old female patient with keratoconus and chronic hydrops cornea referred to the cornea department of our clinic with thin cornea and hydrops in chronic stage and minimal dry eye symptoms. Minimum corneal pachymetry in the right eye was 378 μm as measured by optical coherence tomography(AS-OCT-Zeiss). Atlas corneal topography showed steep K-values 82.60 ax.37 and flat K 75.15 D ax 127 with -7.45 corneal astigmatism. Her best corrected visual acuity was 0.0.5 in right eye and 1.0 in the left eye. Slit lamp examination showed intense punctate epitheliopathy (Figure 1), tear film break-up time (TBUT) was measured as 7-8 sec and Schirmer test was 10 mm in right eye, and the other eye examinations were determined normally.

Results:

The central corneal thickness was improved on the same day of the surgery and vision started to improve 1 week postoperatively. The corneal topography showed a significant decrease in the anterior K1 and K2. The graft in recipient cornea was clearly visible by anterior segment optical coherence tomography observation. The central corneal thickness was stable during the 1-year study period. No complications were observed during the short term follow-up.

Conclusion

In conclusion, this case report is the first study so far that may suggest that this procedure using fresh lenticule with stromal stem cells and live keratocytes safely, reliably, and effectively increases corneal thickness, and improves visual acuity with no adverse effects. This study may provide new avenues in the treatment of corneal ectasia.

Key Words: keratoconus, hydrops, small incision, fresh lenticule, stromal implantation, stromal stem cells, Smile surgery, autologous serum

INTRODUCTION

Keratoconus is typically thought to be a bilateral disease that can be present asymmetrically. It is associated with progressive corneal ectasia and scarring. With no definitive etiology, the corneal ectasia ultimately leads to irregular astigmatism, central anterior scarring and reduced vision.¹ However, biomechanical instability is thought to be one of the main causes. (3)

Hydrops is a rare condition experienced by some keratoconus patients. It is characterized as a tear in the Descemet's membrane and the underlying endothelium, allowing the aqueous humor to leak into the stroma and thus causing stromal edema.² The first case of corneal hydrops in the setting of keratoconus was reported by Plaut in 1900. It was described as a sudden opacity at the apex of the cornea due to a rupture of Descemet's membrane, which was later confirmed by Axenfeld in 1906.² Corneal hydrops occurs in 2.5-3.0% of the population with keratoconus. The majority of cases are unilateral, occur more frequently in males than in females, and typically present in the second or third decade of life.²

Recently, doctors have noticed an increased number of keratoconus patients with allergic symptoms of itching, redness, tearing, chemosis in combination with strings of mucous need intervention. Differentiation between dry eye patients and those who suffer from allergy is important for management of allergy and dry eye in keratoconus patients.

At present, the main operative corrections for keratoconus are corneal collagen cross-linking (CXL) therapy and corneal transplantation. Collagen cross-linking therapy increases the biomechanical stability of the cornea. (4)

However, halting progression resulting from corneal collagen cross-linking may only be transient. (6) Penetrating keratoplasty (PKP) is usually the preferred treatment to improve visual acuity. (7) Nevertheless, the graft survival rate reduces with time postoperatively from 98% to 86% between 1 and 20 years postoperatively, respectively. (8), (9) One of the main challenges to suture-based transplantation in developing countries is the occurrence of a broken suture or infected suture site, which can easily result in infectious keratitis, tissue rejection, or even endophthalmitis due to the lack of access to care or proper ocular medications.

Corneal intrastromal implantation was first described by Barraquer. Many doctors have tested using different materials for intrastromal implantation. This inlay model does not affect the integrity of the corneal epithelium or endothelium. However, the clinical application of this model is limited due to its invasiveness during the creation of the intrastromal pocket, and poor inlay materials. In a previous study, it was shown that there was no implant rejection after auto transplantation nor xenotransplantation using a small-incision femtosecond laser–assisted corneal intrastromal implantation procedure in all rhesus monkeys during a 26-month study period. (10), It was also found that the modified concave inlay lamellae changed corneal refractive power. In the studies by Liu et al, allogeneic lenticules were used to change the refractive power in the animal models.(11),(12),(13) Pradhan et al and Ganesh et al also found that the meniscus allogeneic lenticule from small incision lenticule extraction (SMILE) could reshape the cornea with the necessary precision to correct hyperopia in the recipient.(14) However, the concave lenticule might have more usage in keratectatic diseases, and the use of this inlay allograft corneal implantation model assisted by the femtosecond laser, has not been explored in patients with progressive keratoconus.(15)

In this case report, we performed the SMILE surgery in myopic patients in order to remove the minus dioptre. The fresh lenticule obtained from myopic correction which is thicker in the center and gradually become thinner toward the periphery with a shape of convex –concave positive meniscus lens. We implant this allogenic corneal lamella in human patients with progressive keratoconus and chronic hydrops a few minutes after the SMILE surgery on the donor patient. This case report study showed that the implantation of positive meniscus lenticule is safe, feasible and increases central corneal thickness.

Using of autologous serum in the following months to recuperate the corneal surface was mandatory for this case. Also stopping the use of steroid eye drops for a long time will preserve the eye from its side effects.

Case report

The patient's past ocular history included keratoconus (oval cone in both eyes, OS larger than OD) with long-standing scarring of the right eye, dry eye syndrome, chronic allergic conjunctivitis. The patient denied any past ocular surgery or ocular trauma. Her past medical history was unremarkable, with no use of systemic medications. Her family history was only significant for keratoconus (brother). Her social history was negative for tobacco, alcohol and recreational drug use. She had no known allergies or drug allergies. The manifest refraction and corrected visual acuity (CDVA) was -8.50-6.00x10 (0.08 sc/0.1cc) in the right eye. Corneal topography (Atlas, Carl Zeiss Meditec Jena, Germany) showed steep cornea with increased anterior posterior corneal elevation. The patient was diagnosed with keratoconus, advised that she is not a candidate for refractive surgery. Minimum corneal pachymetry in the right eye was 378 μm as measured by optical coherence tomography (AS-OCT-Zeiss). Atlas corneal topography showed steep K-values 82.60 ax.37 and flat K 75.15 D ax 127 with -7.45 corneal astigmatism. Based on pachymetry and corneal topography, it was decided that lenticule implantation was a more favorable treatment. After a comprehensive discussion with the patient regarding our experience with Relax Smile surgery and lenticule implantation; it was decided to do this procedure. This technique had the potential to be the less invasive, saving the normal structural anatomy. After a written informed consent letter from the donor and the recipient patients in accordance to Declaration of Helsinki, the donor patient received a blood

testing for human immunodeficiency virus, hepatitis B and C viruses, blood glucose, rapid plasma regain, and *Treponema pallidum*. All results were normal.

Surgical Technique

The surgical procedures were performed by the same surgeon under topical anesthesia. The main purpose of the treatment was to increase central corneal thickness in patients with keratoconus and chronic hydrops with minimal scarring in the center. The secondary purpose was to increase visual acuity and to reduce K values.

Donor cornea preparations

The donor and recipient patients were notified and scheduled for the treatment on the same day. The donor patient received a SMILE surgery using VisuMax femtosecond laser. The refractive power of the donor was - 6.00 D with 118 μ m of maximum lenticule thickness. The optical zone (lenticule diameter) and cap diameter were 6.5 and 7.5 mm respectively. After the dissections of both the anterior and posterior planes, the lenticule was extracted through 120-degree superior 3.5 mm-incision and marked with a sterile marker-(Viscot-Medster). The lenticule was put into the BSS solution for ten minutes, then implanted into the recipient eye.

Lenticule implantation technique in recipient patients

Under general anesthesia, the Visumax femtosecond laser flap-cut procedures (Carl Zeiss Meditec AG) with an energy cut index of 30 nJ (150Nj), spot and track spacing surface cuts of 4.5 μ m, spot and track side cuts 2.0 μ m were used to create an intrastromal pocket into the patient's cornea to receive donor lenticule. The stromal pocket diameter was set to 7.6- to 8.0-mm diameter (1 mm larger than the optical zone of the donor lenticule) and the cap thickness was set to 130 μ m from the corneal surface and a 4-mm superior incision. Hinge position flap was set at 90 degrees, hinge angle 50 degree and hinge width 4 mm, side cut angle 90. The pocket was dissected using a blunt spatula, and then washed with normal saline. The lenticule with the anterior aspect facing upward was held with a lenticule forceps, and then gently inserted into the pocket through the 4-mm superior incision. The incision position changes according to the position of the highest K values.

The current orientation was marked with a sterile skin marker. The lenticule was positioned around the marked center of cone and ironed out from the surface using a blunt spatula. (Fig 2). Once centration ending the incision was moved with sterile sponge to remove residual fluid from the interface and no contact lens applied. Postoperatively, antibiotic eye drops (Vigamox), steroid eye drops and lubricant eye drops were prescribed 5 times a day (Maxidex) for a month.

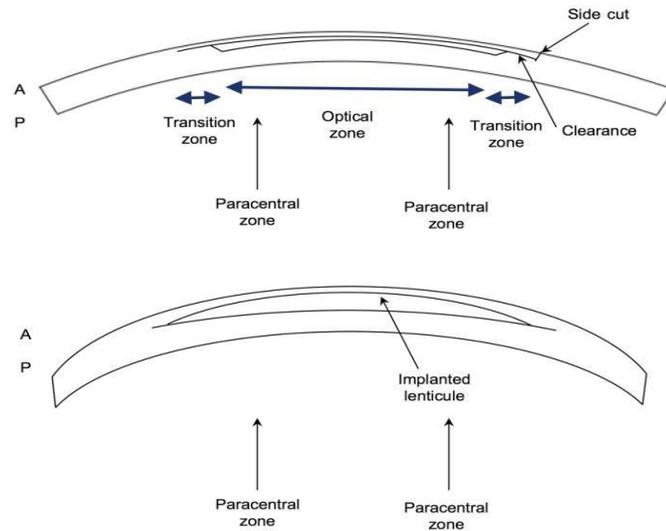


Figure 1. Diagrammatic representation of the steps involving recipient tissue preparation.

A, SMILE lateral view of cornea showing optical (anterior cap) zone (6.5mm diameter), the Clearance zone (1mm wide) and the 120 degrees lenticule side cut C, B. Lenticule shape: Showing the implanted lenticule. A = Anterior Cornea, P= Posterior Cornea

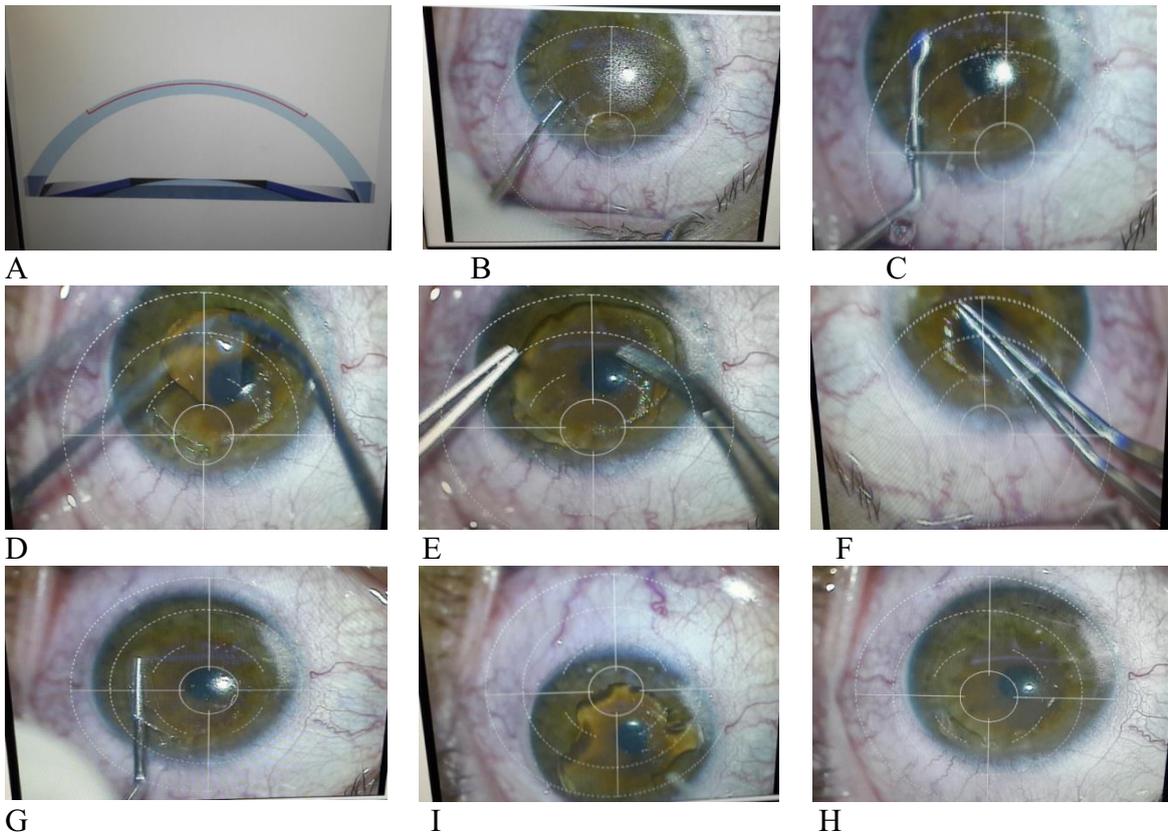


Fig 2. Schematic representation and phases of lenticule implantation in recipient cornea

(A)Using VisuMax free flap to create stromal pocket to implant fresh lenticule, (B) Stromal

pocket in recipient cornea is dissected using blunt small incision spatula, (C) The stromal lenticule was grasped by forceps at this edge and inserted into recipient stromal pocket through small superior temporal incision, (D) The lenticule was distanced into the stromal pocket, (E). After the complete the lenticule distension, it was washed out with saline.

RESULTS

POSTOPERATIVE EXAMINATIONS

1 Day. The patient returned the next morning for a postoperative visit and complained about blurry vision but had no pain or discomfort. Slit-lamp examination revealed minimal corneal edema without stromal haze (Figure 3). The graft was well centered and extended 360° and no adverse effects were seen. Central corneal pachymetry was approximately 787 μm as measured by anterior segment -OCT. The CDVA was 0.08sc/0.05 cc. Postoperatively, antibiotic eye drops (Vigamox ; A) and steroid eye drops (Maxidex;) were prescribed 5 times a day with a tapering dose for 1 month, along with lubricating drops. Follow-ups of patients were conducted for a mean period of 180 ± 13 days (range, 117–193 days).

1 Week. The UDVA improved by 0.1 sc in the right eye. The CDVA was 0.1 cc with manifest refraction of -12.50 -5.25 ax 92. A slit lamp examinations showed improvement without edema as seen in fig 2. Atlas corneal topography showed -5.25 D of corneal astigmatism and central corneal thickness of 538 μm as measured by OCT B scan

1 Month. The UDVA was 0.1 sc. The CDVA was 0.2 cc with manifest refraction of -7.00-2.75x110. A slit lamp examinations showed no corneal edema and a well-arranged lenticule in the stromal pocket. Corneal topography showed continue decrease in corneal astigmatism compared to preoperative values. The corneal pachymetry was 518 μm by corneal OCT.

3 Months. The UDVA was 0.1 sc in the right eye. The CDVA was 0.2 cc with manifest refraction of -7.00-3.00x27. A slit lamp examinations showed a well-centered and well-healed stromal graft and the fresh lenticule was clear. Atlas corneal topography showed -3.25 corneal total astigmatism with K-reading of 56.00 D. Total corneal thickness decreased to 525 μm.

6 Months. The central corneal thickness was stable in right eye. The UDVA was 0.1 sc and CDVA was 0.2 cc with manifest refraction of -6.50-3.50x65. Atlas corneal topography measured K values- Steep K was 48.41 D ax 143 and Flat K was 43.45 D ax 53 with -4.06 corneal astigmatism. As scan be seen in Figure 3, the total corneal thickness arrived at target point before surgery at 496 μm.

1 year. The central corneal thickness was 474 μm. UDVA was 0.1 sc and CDVA was 0.2 cc.

Slit-Lamp Microscopy

There were no intraoperative or postoperative complications at the end of each examination.

The patient tolerated the procedure well.

Slit-lamp examination on day 1 showed mild corneal edema, which subsequently disappeared by day 7.

No reaction, infection, epithelial defects, punctate keratitis, deep lamellar keratitis, or signs of allogeneic rejection were observed in any of the treated eyes by the end of the follow-up period. One month after the operation, the lenticule implantation was well integrated with the surrounding tissue. The boundary of the lenticule was poorly defined but still visible. 3 months after, the boundary of the lenticule was not visible and the cornea was totally clear.

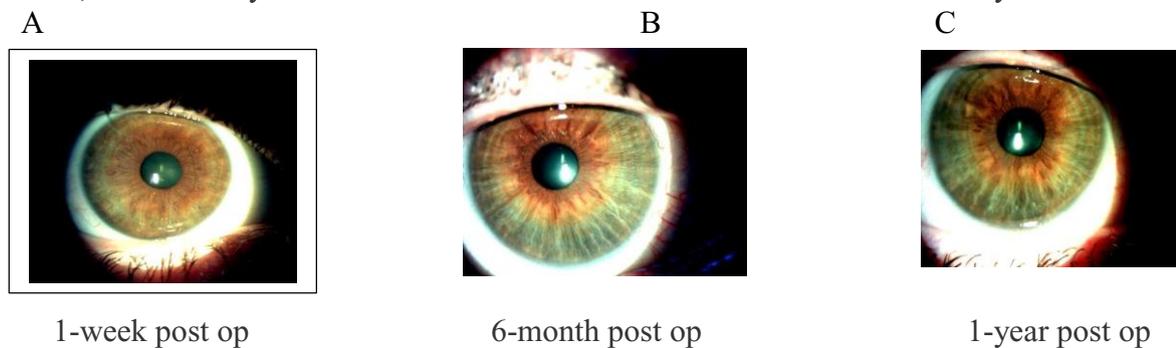


Fig 3. Slit-lamp microscopy photographs of corneas. (A) Preoperative and (B, C and D)

Postoperative features of cornea after stromal lenticule implantation. Cornea shows transparency from 1 week postoperatively.

VISAUL ACUITY AND REFRACTION

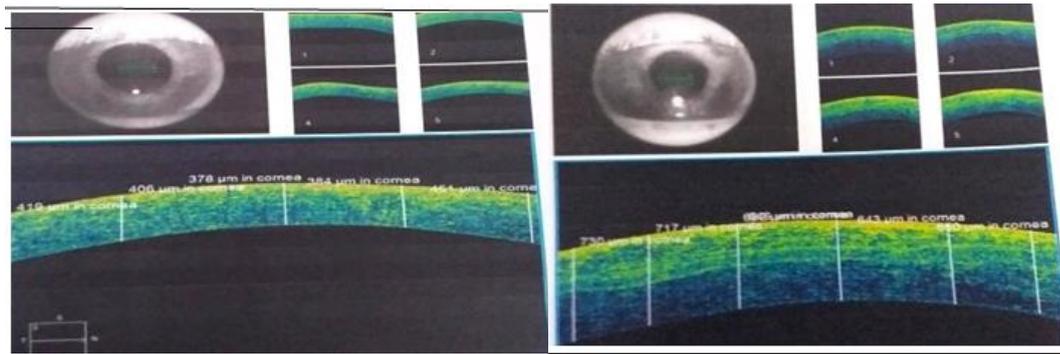
The short term follow-up (6 months after the surgery) showed positive changes in refraction and visual acuity. It was very interesting that patient gained more minus dioptry yet reduced K-value, in addition to improved visual acuity.

Corneal topography

Corneal topography (ATLAS, Zeiss, Meditec, Jena, Germany) showed changes in anterior keratometry values and flattening of the cone.

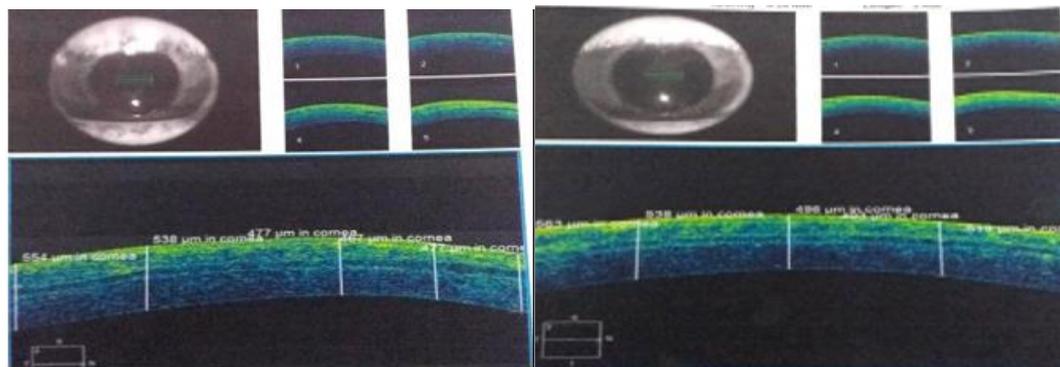
Pachymetry and anterior segment optical coherence tomography

Corneal lenticule implantation was visualized using AS-OCT. The intrastromal lenticule implantation was visible in contrast to the surrounding tissue. At 3 months, the implanted lenticule had a similar density. The boundary of the implanted lenticule was indistinguishable, with the little hyperreflexia. (Fig 6-c). At 6 months, the cornea was clear and transparent, also had the same density as the surrounding tissue. At 1 year postoperative, the density of the lenticule and the cornea still remained the same.



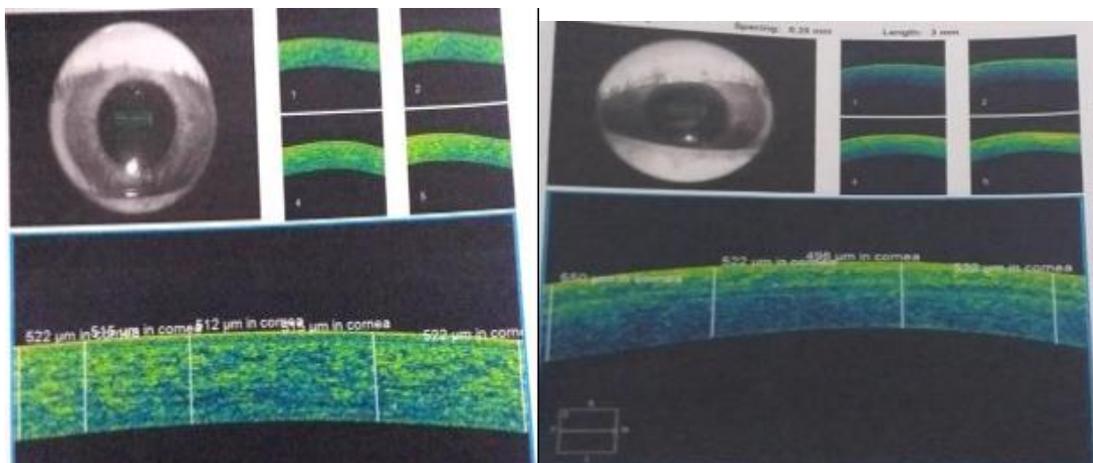
A

B



C

D



E

F

Fig 6. High resolution AS-OCT scan of the recipient cornea. (A) before the lenticule implantation and (B, C, D, E and F) showed 1-day post-op, 1, 3, 6 months and 1 year after surgery. Until the third month, the lenticule interface showed mild hyperreflexia to the surrounding tissue. After 6 months, the lenticule was well integrated with the increase central corneal thickness.

Autologous Serum Tears

The patient was first treated with lubricant tear drops, then with topical autologous serum drops (ASD) for about one year. When ASD is being prepared, approximately 450ml of whole blood is collected by phlebotomy and then allowed to coagulate at room temperature for minimum 2, maximum 4 hours. The coagulated blood is then centrifuged at 3000xg for 15 minutes and the supernatant is removed from the precipitate in sterile conditions [3,4]. After being placed in the droppers, it can be kept at +4 degrees for 1 month and in the freezer for 3 months at 20 degrees in a closed form [3,4]. The drops should be protected from light as vitamin A deteriorates under the light. A significant improvement was observed in the symptoms of the patient who had ASD treatment for 6 months. Also, an evident increase in complaints occurred when the treatment was interrupted. At the last control of the patient, BCVA was 0,1 cc in right eye, TBUT was 10 sec, Schirmer was 10 mm, and there was a mild punctate epitheliopathy on slit lamp examination.

Discussion

More than 90% of the cornea is stroma, a highly organized, transparent connective tissue maintained by keratocytes, quiescent mesenchymal cells of neural crest origin. Unlike keratocytes, the corneal stromal stem cells (CSSCs) undergo extensive expansion in vitro without losing the ability to adopt a keratocyte phenotype. Several lines of evidence suggest CSSCs to be of neural crest line-age and not from bone marrow. CSSCs are localized in the anterior peripheral (limbal) stroma near the stem cells of the corneal epithelium. CSSCs may function to support potency of the epithelial stem cells in their unique limbal niche. On the other hand, little information is available documenting a role for CSSCs in vivo in stromal wound healing or regeneration. In vitro CSSCs reproduce the highly organized connective tissue of the stroma, demonstrating a potential use of these cells in tissue bioengineering. Direct introduction of CSSCs into the corneal stroma generated transparent tissue in a mouse model of corneal opacity. Human CSSCs injected into mice corneas did not elicit immune rejection over an extended period of time. (16)

Recent reports have described a keratocyte stem cell population in the anterior stroma (Du *et al.*, 2005; Funderburgh *et al.*, 2005). Ganesh et al reported 9 patients with hyperopia successfully receiving transplantation of an allogenic cryopreserved lenticule extracted from SMILE, but the stromal collagen fibers of cryopreserved lenticule were damaged because of freezing and thawing.

Autologous serum has been used to treat dry eye syndrome for many years. It contains several growth factors, vitamins, fibronectin and other components that have been considered important for corneal and conjunctival integrity. Serum eye drops are usually prepared as an unpreserved blood solution. The serum is by nature well tolerated and its biochemical properties are somewhat similar to natural tears. Conventional therapeutic options include intensive artificial tear supplements, punctal occlusion, contact lenses, and appropriate management of adnexal disease. The most frequent therapy utilized to treat ocular surface disorders is artificial tear eye drops. However, none of the commercially available artificial tear preparations includes essential tear components such as growth factors, vitamins, and immunoglobulins. Another drawback of artificial tears is the fact that they often contain preservatives, stabilizers, and other additives, which potentially induce toxic or allergic

reactions⁽³⁾. Autologous serum provides growth factors penetrating directly into the stroma affecting good adhesion between the layers of the cornea.

In our case report, the central corneal thickness remained stable, and both CDVA and UDVA improved until 1 year after surgery. Our findings suggest that this surgical procedure can offer long-term stabilization and improve corneal thickness and visual outcomes in those with progressive keratoconus. Using fresh lenticule from donor myopic patients and implanted in recipient corneas with keratoconus through a small incision preserved normal structural anatomy of cornea. In this case series the patient recovered immediately, without complications, and both UDVA and CDVA significantly improved 1 week postoperatively. The target postoperative corneal thickness planned was approximately 470-490 μm , a 95- 100- μm increase from the preoperative pachymetry of 387 μm .

In our case report we used only fresh lenticule that was taken from myopic patients at the same day of surgery, flap less method, stromal stem cell and live keratocytes with preserved anterior corneal lamella and plexus corneal nerves.

Because use of donor stromal lenticules is increasing and new methods for corneal refractive and disease treatment have been reported, it is important to consider a standard procedure for lenticule preparation. Although it is not as important in the current case where improving refraction was not the main outcome measure, like in our project, lenticule preparation is important if the main goal is refractive improvement. For example, Damgaard et al.²⁰ reported standardized lenticule donor tissue preparation by using a 5-hour settling period between removal from the storage solution and excimer laser ablation (17) But in our case series we did not storage longer than ten minutes after Smile surgery from donor patient, during this time we put only in BSS solution. Based on case that was done from Nepal, Pradhan and Reinstein they did only one case with lenticule from donor cornea from eye bank, corneal thickness was 425 μm that differ from our case series. (18)

One of the main challenges to suture-based transplantation in developing countries is the occurrence of a broken suture or infected suture site, which can easily result in infectious keratitis, tissue rejection, or even endophthalmitis due to lack of access to care or proper ocular medications. In addition to an increased risk of infection, careful and thoughtful removal of sutures is an important factor for controlling postoperative astigmatism. (19), (20)

Masterpasqou and his colleagues in their case series adding negative meniscus shape lenticule and it was taken from donor cornea from eye bank. Our opinion is that positive meniscus lenticule offer better opportunities because it is thick in the center and gradually become thinner in the periphery, this cause to increase corneal thickness and balance nasal and temporal side of corneal thickness. Also lenticule thickness offers great advantages over intrastromal corneal ring because the ring is made from synthetic material and side effects like infections, extrusion, halos, glare are reported. In many case due to side effects many patients tend to have ICRS removed after few years. It could reshape the cornea yet it will not increase the corneal thickness. Cross link procedure was no applied in our project because the patient has a corneal thickness under 400 μm , and lenticule implanted with stromal stem cell provide production of keratocytes and the latest give collagen fiber and extracellular matrix that are well organized into recipient corneal stroma.

Conclusion

The present study may suggest that this procedure safely, reliably, and effectively increases corneal thickness and improves visual acuity with no adverse effects. It may even provide new avenues in the treatment of corneal ectasia. Stem cells and live keratocytes are well organized based on cornea transparency and in anterior segment OCT.

This method is an adequate option for patients with keratoconus who need keratoplasty, since it preserves the normal corneal anatomy and the normal anterior lamella. It is a flapless method and the lenticule is fresh from the donor patients, stromal stem cells with live keratocytes without needing to preserve it and healing process is faster.

This new treatment using only SMILE module for donor and recipient patients could be the new step to get the easy way for keratoconus disease because it also have very low cost comparison with penetrating keratoplasty and this method is less invazive, sutureless and more effient than PKP. Treatment with autologous serum is an efficient method to provide a number of growth factors that have been reduced by ocular surface disorders. There is some medical evidence that autologous serum might be clinically effective in some particular ocular surface diseases compared to standard treatment.

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